Therapeutic Protein-Drug Interactions: An FDA Perspective

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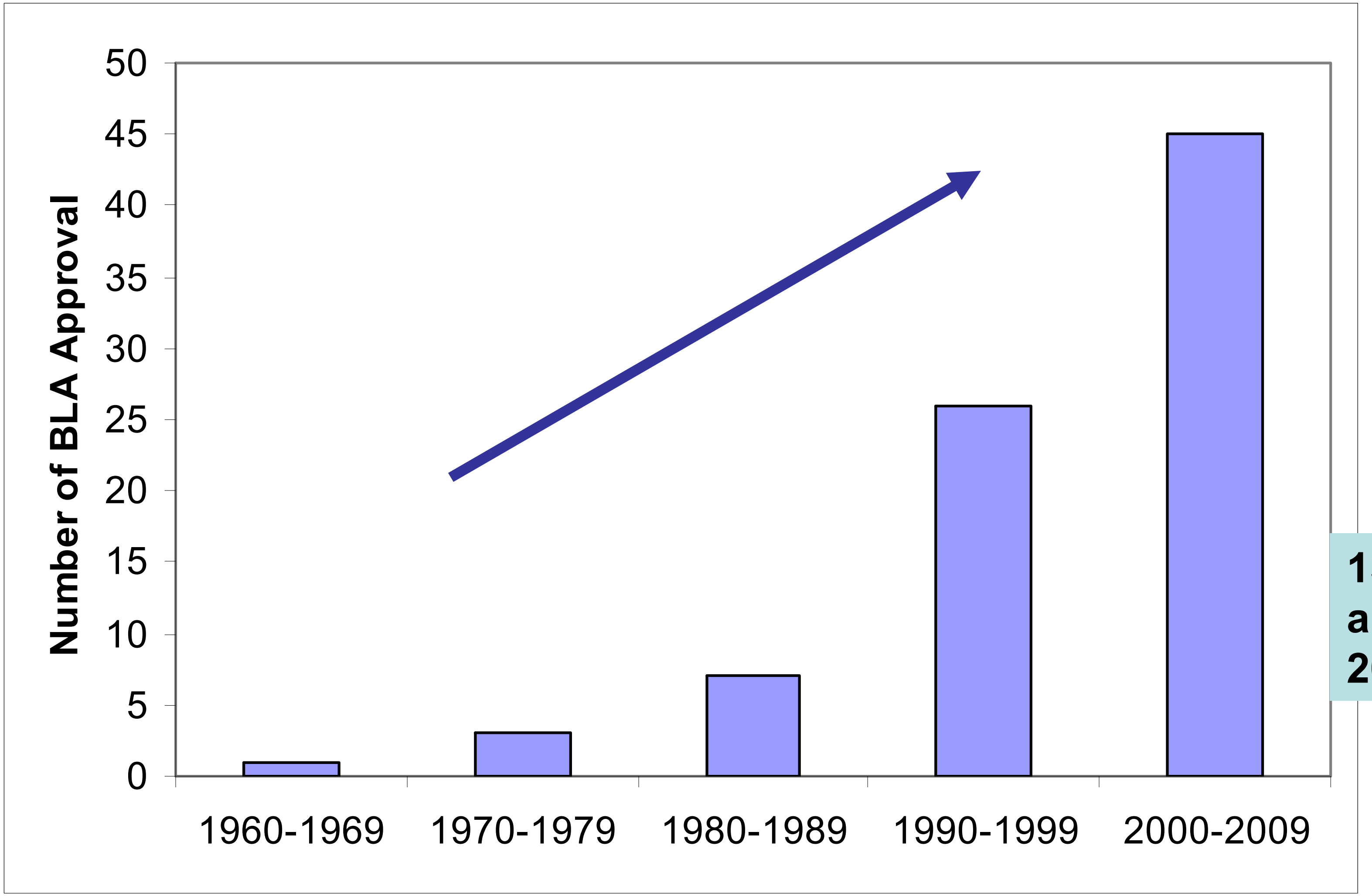
June 4, 2012

Increasing Number of BLA (Biologics License Application) Approvals



2010-2019

13 BLAs approved in 2010-2011

Drug Interactions in Approved BLA Package Inserts (Up to Feb 2010)

	DDI Studies	***Some DDI Information***		***No DDI Information***	***Total***
Cytokines	2	7	**81%**	2	11 (14%)
Enzymes	1	7		9	17 (22%)
Growth Factors	0	2		8	10 (13%)
Monoclonal Antibodies	6	13	**66%**	10	29 (38%)
Misc	0	6		3	9 (12%)
Total	9 **(12%)**	35 **(46%)**		32 **(42%)**	76

Lee I, et al, Clin Pharmacokinetics, 2010

Therapeutic Protein (TP)-Drug (D) Interaction (TP↔D) -Possible Mechanisms

- PK Interaction
  - CYP enzyme modulation (TP→D)
  - Competitive binding
  - Immunosuppression (D→TP)
  - Modulation of target for TP
  - Mechanisms to be elucidated
- PD interaction
  - Antagonism of PD effects
  - Synergistic myelotoxicity, infections, etc.
  - Mechanisms to be elucidated

The 2006 FDA draft DDI guidance covered the drug interaction evaluation for therapeutic proteins -But limited

Classical biotransformation studies are not a general requirement for the evaluation of therapeutic biologics (ICH guidance *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*), although certain protein therapeutics modify the metabolism of drugs that are metabolized by the P450 enzymes. Type I interferons, for example, inhibit CYP1A2 production at the transcriptional and post-translational levels, inhibiting clearance of theophylline. The increased clinical use of therapeutic proteins may raise concerns regarding the potential for their impacts on drug metabolism. Generally, these interactions cannot be detected by in vitro assessment. Consultation with FDA is appropriate before initiating metabolic drug-drug interaction studies involving biologics.

Recent Publicataions on TP-DDI

- Mahmood I, Green MD: Drug interaction studies of therapeutic proteins or monoclonal antibodies. J Clin Pharmacol **2007**;47:1540-1554.
- Seitz K, Zhou H: Pharmacokinetic drug-drug interaction potentials for therapeutic monoclonal antibodies: reality check. J Clin Pharmacol **2007**;47:1104-1118.
- Morgan ET: Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther **2009**;85:434-438.
- Huang SM, Zhao H, Lee JI, Reynolds K, Zhang L, Temple R, Lesko LJ: Therapeutic protein-drug interactions and implications for drug development. Clin Pharmacol Ther **2010**;87:497-503.
- Lee JI, Zhang L, Men AY, Kenna LA, Huang SM: CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. Clin Pharmacokinet **2010**;49:295-310.
- Girish S, Martin SW, Peterson MC, Zhang LK, Zhao H, Balthasar J, Evers R, Zhou H, Zhu M, Klunk L, Han C, Berglund EG, Huang SM, Joshi A: AAPS workshop report: strategies to address therapeutic protein-drug interactions during clinical development. AAPS J **2011**;13:405-416.
- Lloyd P, Zhou H, Theil FP, Kakkar T, Nestorov I, Roberts SA: Highlights From a Recent BIO Survey on Therapeutic Protein-Drug Interactions. J Clin Pharmacol **2011** (E-pub);
- Zhou H, Mascelli MA: Mechanisms of monoclonal antibody-drug interactions. Annu Rev Pharmacol Toxicol **2011**;51:359-372.
- Schmitt C et al. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacol Ther **2011**; 89(5):735-40.
- Kraynov E, Martin SW, Hurst S, Fahmi OA, Dowty M, Cronenberger C, Loi CM, Kuang B, Fields O, Fountain S, Awwad M, Wang D: How current understanding of clearance mechanisms and pharmacodynamics of therapeutic proteins can be applied for evaluation of their drug-drug interaction potential. Drug Metab Dispos **2011**;39:1779-1783.
- Dickmann LJ, Patel SK, Rock DA, Wienkers LC, Slatter JG: Effects of interleukin-6 (IL-6) and an anti-IL-6 monoclonal antibody on drug-metabolizing enzymes in human hepatocyte culture. Drug Metab Dispos **2011**;39:1415-1422.

Not an extensive list.

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541 or Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology

TP-DDI:

Expanded from one paragraph in the 2006 draft guidance

2012 New Draft Guidance Expanded Recommendations on Drug Interaction Evaluation for Therapeutic Proteins

In the Background Section:

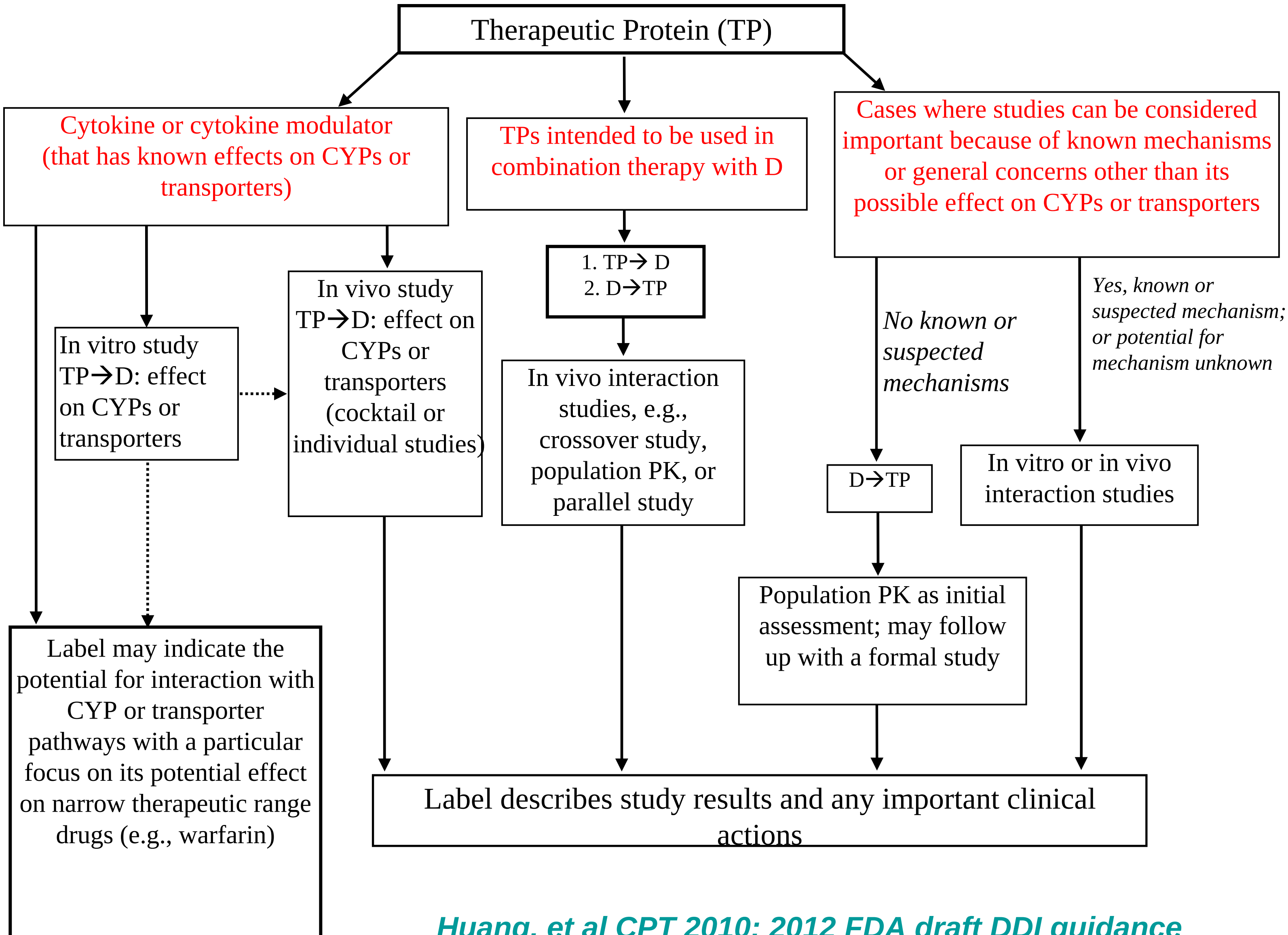
C. Drug Interaction Considerations for Therapeutic Proteins

Therapeutic proteins (TPs) typically do not undergo metabolism or transport as their clearance pathway, therefore the potential is limited for small molecule drugs (termed "drug" in this document) to affect TPs through metabolism or transport pathways. However, a drug may affect the clearance of TPs through the drug's effect on immunogenicity (e.g., methotrexate reduces the clearance of infliximab, possibly due to methotrexate's effect on the antibodies formed against infliximab). In addition, TPs that are cytokines or cytokine modulators may modify the metabolism of drugs that are substrates for P450 enzymes through their effects on the regulation pathways of P450 enzymes. For example, cytokines such as IL-6 can produce concentration-dependent inhibition on various CYP isoforms at the transcription level or by alteration of CYP enzyme stability in patients with infection or inflammation, and increase the plasma concentrations of specific CYP substrate drugs. In contrast, cytokine modulators such as tocilizumab (anti-IL-6 receptor antibody) may reverse the apparent "inhibition" effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP activities.

General points to be considered for evaluation of TP-drug interactions are discussed in **section IV.B.2.**

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Figure 7-Summarizes the Thought Process to Consider TP-DDI Evaluation (Section IV.B.2.)



Huang, et al CPT 2010; 2012 FDA draft DDI guidance

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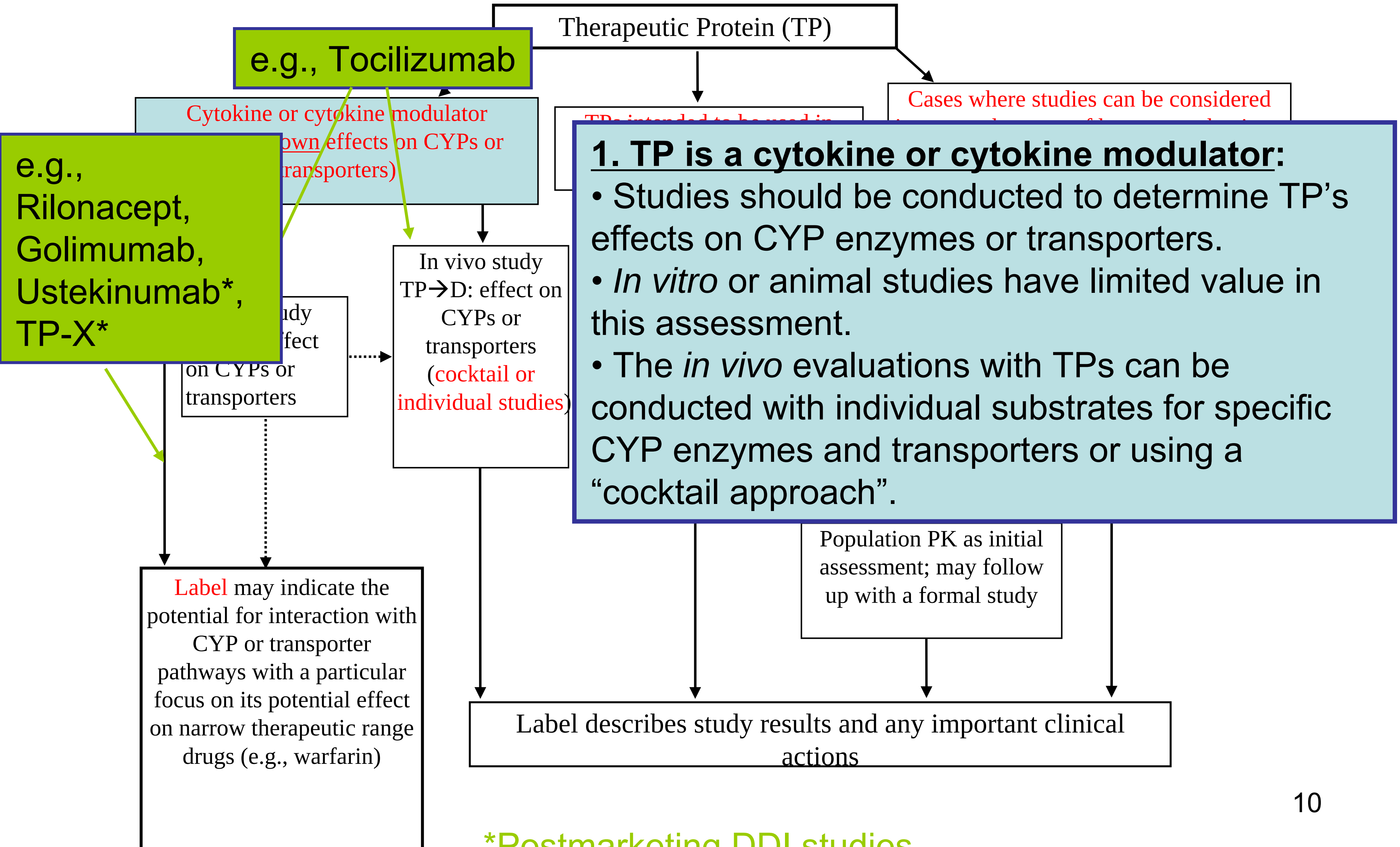


1. TP is a cytokine or cytokine modulator:

- Studies should be conducted to determine TP's effects on CYP enzymes or transporters.
- *In vitro* or animal studies have limited value in this assessment.
- The *in vivo* evaluations with TPs can be conducted with individual substrates for specific CYP enzymes and transporters or using a "cocktail approach".

*Postmarketing DDI studies

Tocilizumab Label (1)
(IL-6R blocker)

7.2 Interactions with CYP450 Substrates

- Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effects on CYP2C8 or transporters is unkown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively.

With *in vitro* and clinical DDI studies

Tocilizumab Label (2)
(IL-6R blocker)

7.2 Interactions with CYP450 Substrates (Cont'ed)

- The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

With *in vitro* and clinical DDI studies

Golimumab Label
(TNF blocker)

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFa) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzyes could be normalized. Upon initiation or discontinuation of SIMPONI in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophyllne) is recommended and the individual dose of the drug product may be adjusted as needed.

With no *in vitro* nor clinical DDI studies

Ustekinumab
(Human IL-12/IL-23 Antagonist)

- **Post-marketing requirement (2009)**
  - “Conduct an *in vitro* study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes. If, upon review, there is no marked modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary.”

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/125261s000ltr.pdf

Ustekinumab
Labeling Update (May 2012)

12.3 Pharmacokinetics

Drug-Drug Interactions

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the clinical relevance of *in vitro* data has not been established *[see Drug Interactions (7.3)]*.

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA®, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA® in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

http://www.stelarainfo.com/pdf/PrescribingInformation.pdf

CYP enzyme modulation by cytokines or cytokine modulators

- We have communicated to sponsors during IND to study TP-DDI for TPs that are cytokine or cytokine modulators (especially those with known effect on CYPs)

- Labeling for TPs that are related to the following cytokines has included DDI language (with or without dedicated studies for P450 substrate drugs):
  - IL-1β, IL-6, IL-12/IL-23, TNF, INF

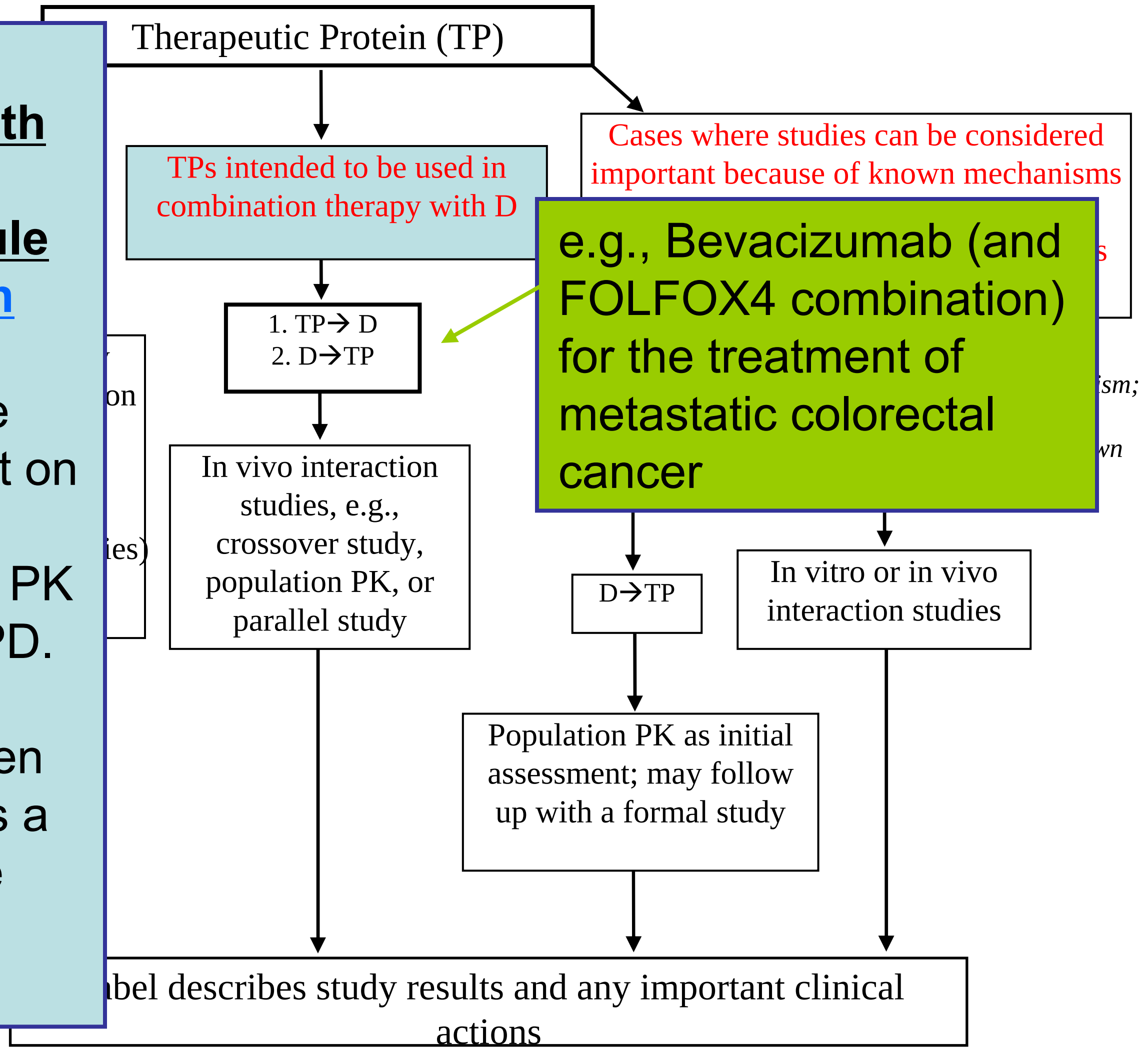
References (recent reviews that have labeling examples on TP-DDI):
Lee et al Clin Pharmacokinetics, 2010; Huang et al CPT, 2010;
Girish et al AAPS Journal 2011; Zhao et al, TP-DDI book chapter, 2012

Figure 7-Summarizes the Thought Process to Consider TP-DDI Evaluation (Section IV.B.2.)

2. For TPs that will be used in combination with other drug products (small molecule or TP) as a combination therapy:

• Studies should evaluate the effect of each product on the other. The studies should assess effects on PK and, when appropriate, PD.

• This evaluation is particularly important when the combination drug has a narrow therapeutic range (e.g., chemotherapeutic agents).

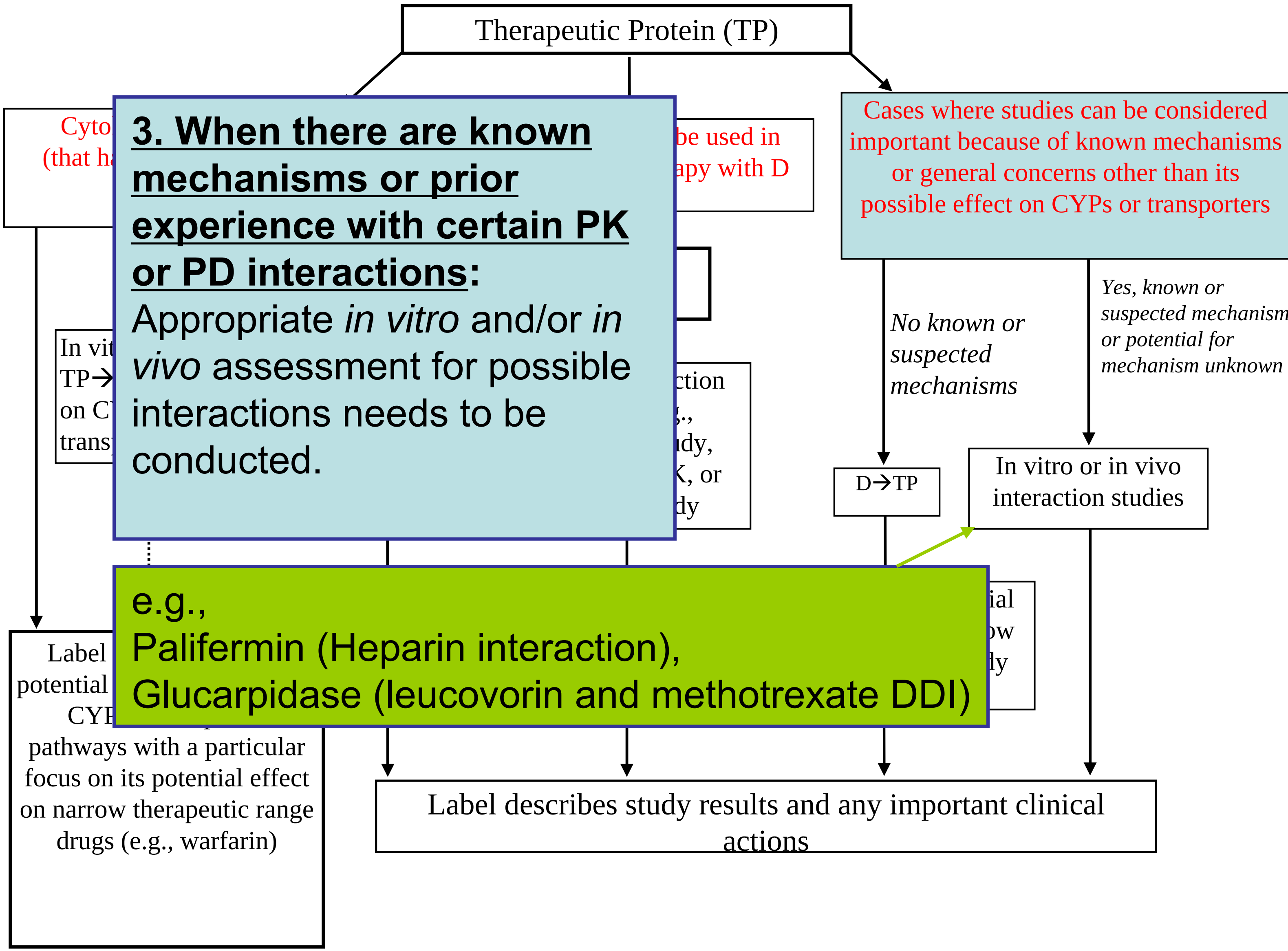


e.g., Bevacizumab (and FOLFOX4 combination) for the treatment of metastatic colorectal cancer

TP used in combination with other drug products (combination therapy)

- Examples include cancer therapies where multiple drug treatments are combined
  - Bevacizumab in combination with FOLFOX4 for the treatment of metastatic colorectal cancer
  - Trastuzumab + doxorubicin, cyclophosphamide + paclitaxil or docetaxil or + docetaxil and carboplatin for adjuvant treatment of HER2 overexpressing node positive or node negative (estrogen/progesterone receptors (ER/PR) negative or with one high risk feature) breast cancer
- Effect of TP on chemotherapy drugs are usually studied during drug development
  - Many chemotherapy drugs have narrow therapeutic range

Figure 7-Summarizes the Thought Process to Consider TP-DDI Evaluation



Interaction between Palifermin and Heparin (Competitive Binding)

- Changes in palifermin PK:
  - 5-fold ↑ in AUC,
  - 80% ↓ in CL,
  - 74% ↓ in Vss,
  - doubled t½
- No effect of palifermin on heparin activity (aPTT)
- Effect of heparin on palifermin efficacy and safety was determined in a post-marketing study.

Palifermin Label

7 DRUG INTERACTIONS

In vitro and *in vivo* data suggests that palifermin interacts with unfractionated as well as low molecular weight heparins. Heparin co-administration resulted in a 5-fold increase in palifermin systemic exposure. Avoid coadministration of palifermin with heparin. If heparin is used to maintain an intravenous line, rinse the line with saline prior to and after Kepivance administration.

Other Mechanisms

What's Known in the past	**What can be done for "new" drugs**
Effect of methotrexate (MTX) on infliximab and adalimumab immunogenicity and exposure	Study effect of MTX on a new TNF blocker and include results in the label (e.g., golimumab)
Increased infections with concurrent therapy, e.g., etanercept and anakinra, etanercept and Abatacept	Include a warning in a new TNF blocker's label about a higher risk of serious infections with anakinra or abatacept (e.g., golimumab)

TP-DDI Summary

- TP-drug interactions should be evaluated for
  - cytokines and cytokine modulators
  - combination agents
  - mechanism indicated

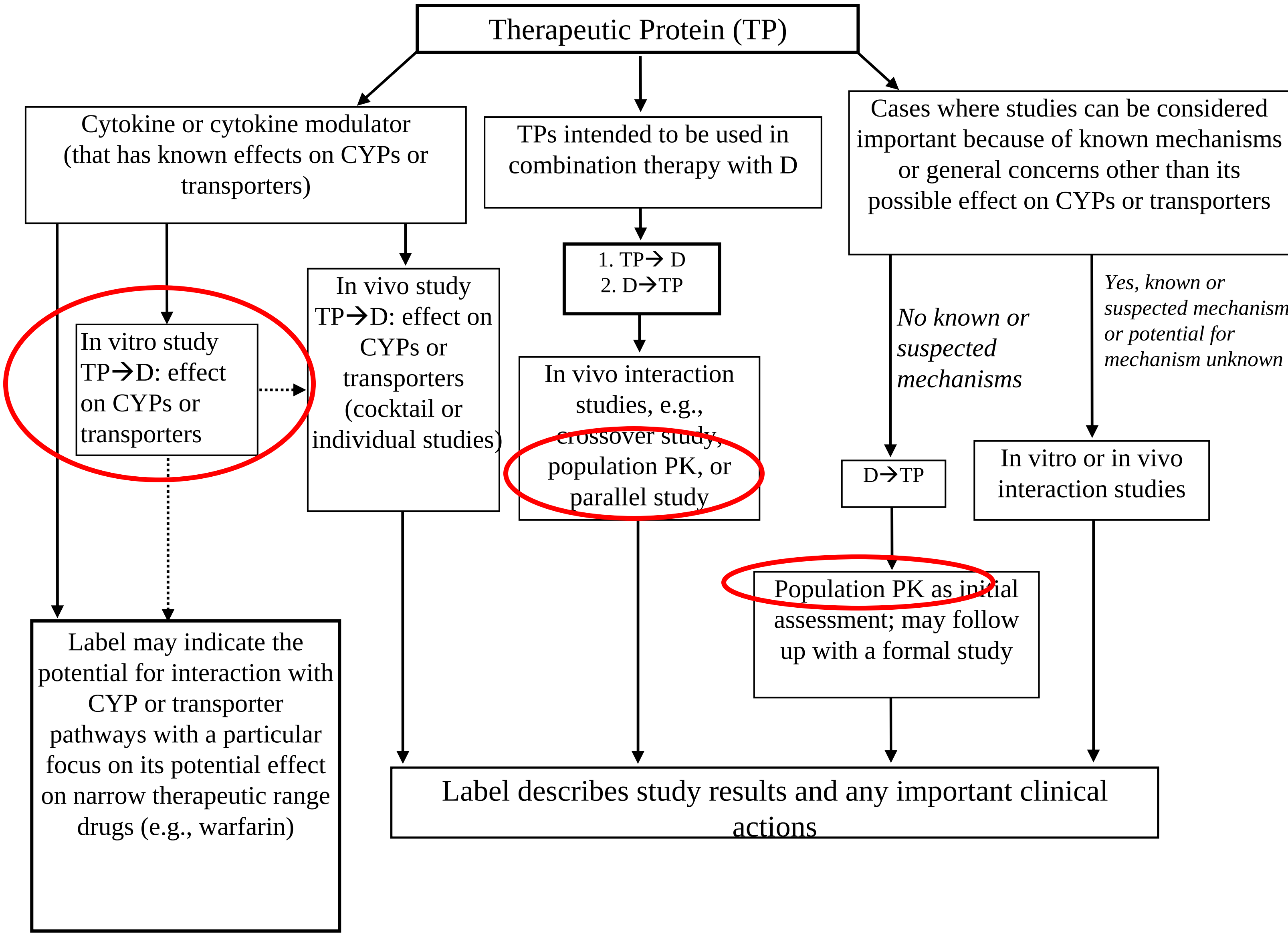
Comments Received on the 2012 FDA Draft DDI Guidance (as of May 31, 2012)

- 26 comments
  - PhRMA, BIO, IQC
  - Abbott, Actelion, Amgen, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Genentch/Roche, Gilead, GSK, Jassen, Merck, Novartis, Pfizer, Sanofi
  - Absorption Systems, Advion, SimCYP
  - Individuals (2)
- 1 Publication on induction (Puracyp)

Some comments related to TP-DDI…

- "Cytokine or cytokine modulator" too broad→ limit to "proinflammatory…"
- "In vitro box evaluation" in Figure 7
  - Remove
  - On a case by case basis, appropriate in vitro assays can guide clinical DDI decision
  - Clarify whether required
- Oncology (chemotherapy) should be made as an exception
- How to interpret the 3rd box on the right?
- Include a table of known TP-DDI with reported magnitude of changes
- Should not recommend TP-DDI until preclinical methodology is ready
- Timing of TP-DDI
- Provide guidance on TP-DDI study design
- ….

Figure 7-Summarizes the Thought Process to Consider TP-DDI Evaluation (Section IV.B.2.)



TP-DDI Evaluation

- Understand biology of TP and disease
  - Which cytokines regulate which P450s *in vivo*, in which diseases?
  - How TP is cleared?
- *In vitro* methodology **(Day 2)**
  - Which system? Which cytokine? Experiment controls?
- Clinical study design
  - Many may need to be conducted in patients
    - dedicated vs. part of Phase 2/3?
  - Which patient population may be more sensitive to cytokine modulation? Effect of disease severity?
  - Utilization of POP-PK?

Acknowledgements

- Shiew-Mei Huang
- Yow-Ming Wang
- Hong Zhao
- Office of Clinical Pharmacology
- IQC-FDA TP-DDI subworkgroup members